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09/710,444	11/10/2000	Lutz Riechmann	8654/1090	5253

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EXAMINER	
STEELE, AMBER D	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/710,444	RIECHMANN ET AL.	
	Examiner	Art Unit	
	Amber D. Steele	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 October 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,5-7,9-15 and 17-26* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,5-7,9-15 and 17-26* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/2/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. The amendment received on April 10, 2006 amended claims 1-3, 8-9, and 20 and canceled claim 4.

The amendment received on March 1, 2007 amended claims 1, 3, 9, and 11 and canceled claims 2 and 8.

The amendment received on October 19, 2007 amended claims 1, 3, 5, 7, 9-10, 17, 19, and 21; canceled claim 16; and added new claims 22-26.

Claims 1, 3, 5-7, 9-15, and 17-26 are currently pending and under consideration.

Priority

2. The present application claims status as a CON of PCT/GB99/01526 05/13/1999. In addition, the present application claims foreign priority to United Kingdom 9810223.9 and United Kingdom 9810228.8.

Invention as Claimed

3. A method for the selection of a bacteriophage comprising the steps of: (a) providing a virus comprising a plurality of bacteriophage encoding and displaying a fusion polypeptide, said fusion polypeptide comprising a heterologous polypeptide inserted into the sequence of a bacteriophage coat protein polypeptide, wherein said plurality of bacteriophage comprise a sequence specific protease cleavable site located within the displayed polypeptide and which site

is protected by folding of the polypeptide and is otherwise either absent from the bacteriophage, or inaccessible to cleavage, or present only in bacteriophage proteins not required after bacteriophage assembly to mediate infection and wherein cleavage of said sequence specific protease cleavable site impairs infection by a said bacteriophage; (b) exposing the bacteriophage to a protease that recognizes said sequence specific protease cleavable site, wherein said protease only cleaves said sequence specific protease cleavable site if said fusion polypeptide is not properly folded, such that said exposing selects against phage displaying fusion polypeptide that is not properly folded; and (c) propagating a bacteriophage comprising intact fusion polypeptide.

Claim Objections

4. Claims 1, 3, 5-7, 9-15, and 17-26 are objected to because of the following informalities:

A. Claim 1 is objected to due to the redundancy of the phrase "bacteriophage coat protein polypeptide" in method step a, line 3. The phrase "bacteriophage coat protein" is suggested.

B. Claim 1 is objected to due to a lack of consistency between terms. See method step a, line 5. Utilizing "displayed fusion polypeptide" instead of "displayed polypeptide" is suggested.

C. Claim 1 is objected to due to a lack of consistency between terms. See method step b, line 4. Utilizing "bacteriophage" instead of "phage" is suggested.

D. Claim 5 is objected to. The claim should read "wherein the virus encodes a repertoire of sequences" or "wherein the plurality of bacteriophage encode a repertoire of sequences". This is necessary because the virus is utilized to denote a population (i.e. a

plurality of bacteriophage; see claim 1) which would encode multiple sequences. While it is recognized that a single bacteriophage also encodes multiple polypeptides, the objection is made based on the nature of the invention in the specification (i.e. a single heterologous polypeptide or a single fusion polypeptide displayed on each bacteriophage; multiple heterologous polypeptides or multiple fusion polypeptides displayed in a plurality of bacteriophage). See page 3, lines 19-23 of the present specification wherein virus is defined as both the plural and singular form.

E. Claims 5-6 are objected to due to inconsistency between claims. Claim 5 reads that bacteriophage (i.e. virus; see section D above) encodes a repertoire of sequences while claim 6 reads that the repertoire of sequences encodes the displayed heterologous polypeptide. Thus, it is unclear if the repertoire of sequences are polypeptides or polynucleotides.

F. Claim 6 is objected to due to the inconsistency between claims. The claim should read "heterologous polypeptide" (i.e. genus) instead of "heterologous peptide or protein" (i.e. species).

G. Claim 9 is objected to due to the inconsistency between claims. The claim should read "fusion polypeptide" (i.e. genus) instead of "fusion protein or polypeptide" (i.e. species and genus).

H. Claim 10 is objected to the inconsistency between claims (please note: claim 10 depends from claim 9 which depends from claim 1 whereas claims 5-7 recite repertoire of sequences). The phrase "some fusion polypeptides" instead of "some members of the repertoire" is suggested.

I. Claim 11 is objected to due to the inconsistency between claims (please note: claim 11 depends from claim 9 which depends from claim 1 whereas claims 5-7 recite repertoire of sequences). The phrase "some fusion polypeptides" instead of "some members of the repertoire" is suggested.

J. Claim 14 is objected to due to the inconsistency between terms. The phrase "heterologous polypeptide" or "fusion polypeptide" instead of "protein or polypeptide" is suggested.

K. Claim 15 is objected to due to the inconsistency between terms. The phrase "fusion polypeptides" instead of "proteins" is suggested.

Appropriate correction is required.

Withdrawn Rejections

5. The rejection of claims 1, 3, 5-7 and 9-21 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is withdrawn in view of the amendments to the claims received on October 19, 2007 (i.e. bacteriophage, sequence specific protease cleavable site, etc.).

6. The rejection of claims 1, 3, 5-7, and 9-21 under 35 U.S.C. 112, first paragraph (scope of enablement) is withdrawn in view of the amendments to the claims received on October 19, 2007 (i.e. bacteriophage, sequence specific protease cleavable site, etc.).

New Rejection Necessitated by Amendment

Claim Rejections - 35 USC § 112

7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

8. Claim 21 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of selection of a bacteriophage comprising exposing the virus to trypsin, thermolysin, subtilisin, Glu-C, or chymotrypsin, the specification does not reasonably provide enablement for a method of selection of a bacteriophage utilizing factor Xa, Arg-C, or thrombin (see Example 2, page 15). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. This is a **scope of enablement** rejection.

There are many factors to consider when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any experimentation is "undue". These factors include, but are not limited to:

1. The breadth of the claims;
2. The nature of the invention;
3. The state of the prior art;
4. The level of skill in the art;
5. The level of predictability in the art;
6. The amount of direction provided by the inventor;
7. The presence or absence of working examples;
8. The quantity of experimentation necessary needed to make or use the invention based on the disclosure.

See *In re Wands* USPQ 2d 1400 (CAFC 1988):

<u>The breadth of the claims and the nature of the invention</u>:

The claims include any bacteriophage that can express a fusion polypeptide; any sequence specific protease cleavable sites comprising Lys (K), Arg (R), Phe (F), Trp (W), Tyr (Y), Leu (L), Gly (G), Ala (A), Val (V), Ile (I), Ser (S), Thr (T), Glu (E), Arg-Gly, and Ile/Leu-Glu-Gly-Arg; the following proteases: trypsin, thermolysin, subtilisin, Glu-C, chymotrypsin, factor Xa, Arg-C, and thrombin; any fusion polypeptide; any bacteriophage coat protein; and any heterologous polypeptide. Accordingly, the claims encompass the selection of a vast number of bacteriophage expressing a vast number of fusion polypeptides. Accordingly, the claim scope is broad with respect to encompassed polypeptides, bacteriophage, and sequence specific cleavage sites.

The state of the prior art and the level of predictability in the art:

While the state of the art and level of predictability for the expression of fusion proteins in virus particles (e.g. phage display) and screening assays based on binding is high, the art in July 1998 reported that not all cleaving agents produced the expected result of decreasing viral infectivity (i.e. factor Xa, Arg-C, and thrombin). Kristensen and Winter (Folding & Design 3: 321-328, 1998) teach that a cleavage site with several proteolytic sites was susceptible to cleavage by trypsin, thermolysin, subtilisin, Glu-C, and chymotrypsin but infectivity of the virus was not altered by Factor Xa, Arg-C, or thrombin even though potential cleavage sites were present (please refer to pg. 322). Please also refer to Example 2 of the present specification.

The level of skill in the art:

The level of skill would be high, most likely at the Ph.D. level.

The amount of direction provided by the inventor and the existence of working examples:

The specification specifically teaches that Factor Xa, Arg-C, and thrombin are non-enabled embodiments (see Example 2, page 15).

The quantity of experimentation needed to make or use the invention based on the content of the disclosure:

In light of the unpredictability surrounding the claimed subject matter, the undue breadth of the claimed invention's intended use, and the lack of adequate guidance, one wishing to practice the presently claimed invention would be unable to do so without engaging in undue experimentation. One wishing to practice the presently claimed invention would have to produce Factor Xa, Arg-C, and thrombin specific sequences; insert the sequences in various positions of the bacteriophage coat proteins; utilize multiple bacteriophage; and would still not be assured of even one successful propagation of a bacteriophage displaying a properly folded protein via the method (i.e. propagation of bacteriophage displaying both properly folded and improperly folded proteins). In addition, it is noted that the Arg (R) of SEQ ID NO: 1 was susceptible to trypsin cleavage, but not to Arg-C cleavage suggesting that there is not a clear reason why one protease would work and not the other (i.e. no starting point is clear for experiments to rectify the problem).

Therefore, the presently claimed invention is not enabled for the scope of the claimed method.

Arguments and Response

9. Please note: the above rejection is a new rejection necessitated by amendment. However, the rejection is similar to the previous enablement rejection. Thus, arguments to the previous enablement rejection that pertain to the new enablement rejection are addressed below.

Applicants' arguments directed to the rejection under 35 USC 112, first/second paragraph (enablement), for claim 21 was considered but are not persuasive for the following reasons.

Applicants contend that pGEX vectors were commercially available at the time of filing (i.e. comprise thrombin, Factor Xa, and PreScission™ protease cleavage sites) and one of skill in the art would be able to design protease cleavage sites for use in the claimed method. In addition, applicants contend (i.e. regarding the Kristensen and Winter reference) that "[t]he results in Table 1 of the reference clearly demonstrate that Kristensen and Winter likely could have modified conditions to promote cleavage by Factor Xa, Arg-C, or thrombin, but that there was no reason to spend the money, time, or resources on such an endeavor" (see page 16, first full paragraph, last sentence of the response received on October 19, 2007).

Applicants' arguments are not convincing since the Kristensen and Winter reference and the present specification utilized sequences with Factor Xa, Arg-C, and thrombin specific cleavage sequences without successs (i.e. not enabled; see page 322, right column, lines 5-8 of Kristensen and Winter and Example 2 of the present specification). SEQ ID NO: 1 (PAGLSEGSTIEGRGAHE) comprises trypsin, chymotrypsin, thermolysin, Glu-C, Factor Xa, Arg-C, and thrombin cleavage sites. For example, the Factor Xa cleavage site (i.e. IEGR of SEQ ID NO: 1; PAGLSEGSTIEGRGAHE) comprises the trypsin cleavage site (i.e. R of SEQ ID NO: 1; PAGLSEGSTIEGRGAHE) and the Arg-C cleavage site (i.e. R of SEQ ID NO: 1; PAGLSEGSTIEGRGAHE). However, Factor Xa and Arg-C are not functional in the present method while trypsin is. Thus, it is not clear why one protease is functional while the other two proteases are not and applicants have not provided any enabling information regarding how Factor Xa, Arg-C, and thrombin could be made functional in the present method. Furthermore,

applicants' arguments regarding "there was no reason to spend the money, time, or resources on such an endeavor" suggest that the amount of experimentation would be "undue" (i.e. time consuming, expensive, and labor intensive) which further supports the lack of enablement for Factor Xa, Arg-C, and thrombin in the presently claimed method.

The information contained in the disclosure of an application must be sufficient to inform those skilled in the relevant art how to both make and use the claimed invention. However, the present specification does not teach one of skill in the art how to make Factor Xa, Arg-C, and thrombin specific cleavage sequences which work in the presently claimed method (see Example 2).

The arguments of counsel cannot take the place of evidence in the record. See *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997); and MPEP § 2145.

10. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 1, 3, 5-7, 9-15, and 17-26 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "the polypeptide" in method step a, line 5. There is insufficient antecedent basis for this limitation in the claim. Either "the heterologous polypeptide" or "the fusion polypeptide" is suggested.

Conclusion

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Future Communications

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Amber D. Steele whose telephone number is 571-272-5538. The examiner can normally be reached on Monday through Friday 9:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Doug Schultz can be reached on 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

ADS
January 14, 2008

/Jon D. Epperson/
Primary Examiner, AU 1639